Table 17. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations

17a. Potentially Life-Threatening and Serious Adverse Events

Adverse effects	Causative ARVs	Onset/clinical manifestation	Estimated frequency	Risk Factors	Prevention/ monitoring	Management
POTENTIALLY LIFE-THREATENING ADVERSE EFFECTS (Listed in alphabetical order)						
Hepatic Events (nevirapine-associated symptomatic events, including hepatic necrosis)	NVP	Onset: Greatest risk within 1st few weeks of therapy; can occur through 18 weeks Symptoms: Abrupt onset of flu-like symptoms (nausea, vomiting, myalgia, fatigue), abdominal pain, jaundice, or fever with or without skin rash; may progress to fulminant hepatic failure with encephalopathy Approximately 1/2 of the cases have accompanying skin rash Some may present as part of DRESS syndrome (drug rash with eosinophilia and systemic symptoms)	Symptomatic hepatic events: • 4% overall (2.5%-11% from different trials) • In women - 11% in those w/ pre-NVP CD4 >250 cells/mm^3 vs. 0.9% w/ CD4 <250 cells/mm^3; • In men - 6.3% w/ pre-NVP CD4 >400 cells/mm^3 vs. 2.3% w/ CD4 <400 cells/mm^3	•Higher CD4 T cell count at initiation (>250 cells/mm^3 in women & >400 cells/mm^3 in men) •Female gender (including pregnant women) •Elevated ALT or AST at baseline; •HBV and/or HCV co-infection; •Alcoholic liver disease •HIV (-) individuals when NVP is used for post-exposure prophylaxis •High NVP concentration	•Avoid initiation of NVP in women w/ CD4 >250 cells/mm^3 or men w/ CD4 >400 cells/mm^3 unless the benefit clearly outweighs the risk •Counsel pts re: signs & symptoms of hepatitis; stop NVP & seek medical attention if signs & symptoms of hepatitis, severe skin rash, or hypersensitivity reactions appear •Monitoring of ALT & AST (every 2 weeks x 1st month, then monthly x 3 months, then every 3 months •Obtain AST & ALT in patients with rash •2-week dose escalation may reduce incidence of hepatic events	•Discontinue ARV including nevirapine (caution should be taken in discontinuation of 3TC, FTC, or TDF in HBV co-infected patients) •Discontinue all other hepatotoxic agents if possible • Rule out other causes of hepatitis • Aggressive supportive care as indicated **Note:** Hepatic injury may progress despite treatment discontinuation. Careful monitoring should continue until symptom resolution. **Do not rechallenge patient with NVP** The safety of other NNRTIs (EFV or DLV) in patients who experienced significant hepatic event from NVP is unknown – use with caution.
Lactic acidosis/ hepatic steatosis +/- pancreatitis (severe mitochondrial toxicities)	NRTIs, esp. d4T, ddI, ZDV	Onset: months after initiation of NRTIs Symptoms: • Initial onset may be insidious with nonspecific gastrointestinal prodrome (nausea, anorexia, abdominal pain, vomiting), weight loss, and fatigue; • Subsequent symptoms may be rapidly progressive with tachycardia, tachypnea, hyperventilation, jaundice, muscular weakness, mental status changes, or respiratory distress • Some may present with multi-organ failure, such as fulminant hepatic failure, acute pancreatitis, encephalopathy, and respiratory failure Laboratory findings: • Increased lactate (often > 5 mmole) • Low arterial pH (some as low as < 7.0) • Low serum bicarbonate • Increased anion gap • Elevated serum transaminases, prothrombin time, bilirubin • Low serum albumin • Increase serum amylase & lipase in patients with pancreatitis • Histologic findings of the liver – microvesicular or macrovesicular steatosis	Rare One estimate 0.85 cases per 1000 patient-years Mortality up to 50% in some case series, (esp. in patients with serum lactate > 10 mmole)	•d4T + ddI •d4T, ZDV, ddI use (d4T most frequently implicated) •Long duration of NRTI use •Female gender •Obesity •Pregnancy (esp. with d4T+ddI) •ddI + hydroxyurea or ribavirin •High baseline body mass index	•Routine monitoring of lactic acid is generally not recommended; •Consider obtaining lactate levels in patients with low serum bicarbonate or high anion gap and with complaints consistent with lactic acidosis; •Appropriate phlebotomy technique for obtaining lactate level should be employed	•Discontinue all ARVs if this syndrome is highly suspected (diagnosis is established by clinical correlations, drug history, and lactate level) •Symptomatic support with fluid hydration •Some patients may require IV bicarbonate infusion, hemodialysis or hemofiltration, parenteral nutrition or mechanical ventilation •IV thiamine and/or riboflavin – resulted in rapid resolution of hyperlactatemia in some case reports **Note:** •Interpretation of high lactate level should be done in the context of clinical findings. •The implication of asymptomatic hyperlactatemia is unknown at this point **ARV treatment options**: •May consider using NRTIs with less propensity of mitochondrial toxicities – (e.g., ABC, TDF, 3TC, FTC) – should not be introduced until lactate returns to normal. •Recommend close monitoring of serum lactate after restarting NRTIs •Some consider using NRTI-sparing regimens with PI + NNRTI +/- FI (e.g., IDV + EFV, LPV/r + EFV, etc)– efficacy and benefit of this type of regimen unknown, but currently under investigation

Table 17. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations

17a. Potentially Life-Threatening and Serious Adverse Events (continued)

Adverse effects	Causative ARVs	Onset/clinical manifestation	Estimated frequency	Risk Factors	Prevention/ monitoring	Management
POTENTIALLY LIFE-THREATENING ADVERSE EFFECTS (Listed in alphabetical order)						
Lactic acidosis/ Rapidly progressive ascending neuromuscular weakness	Most frequently implicated ARV: d4T	Onset: months after initiation of ARV; then dramatic motor weakness occurring within days to weeks Symptom: very rapidly progressive ascending demyelinating polyneuropathy, may mimic Guillain-Barré Syndrome; some patients may develop respiratory paralysis requiring mechanical ventilation; resulted in deaths in some patients Laboratory findings may include: •Low arterial pH •Increased lactate •Low serum bicarbonate •Increased anion gap •Markedly increased creatine phosphokinase	Rare	Prolonged d4T use [found in 61 of 69 (88%) cases in one report]	Early recognition and discontinuation of ARVs may avoid further progression	•Discontinuation of ARVs •Supportive care, including mechanical ventilation if needed (as in cases of lactic acidosis listed previously) •Other measures attempted with variable successes: plasmapheresis, high dose corticosteroid, intravenous immunoglobulin, carnitine, acetylcarnitine •Recovery often takes months – ranging from complete recovery to substantial residual deficits •Symptoms may be irreversible in some patients **Do not rechallenge patient with offending agent**
Stevens-Johnson Syndrome (SJS)/ Toxic epidermal necrosis (TEN)	NVP > EFV, DLV; Also reported with: APV, f-APV, ABC, ZDV, ddI, IDV, LPV/r, ATV	Onset: first few days to weeks after initation of therapy Symptoms: *Cutaneous involvement:* •Skin eruption with mucosal ulcerations (may involve orogingival mucosa, conjunctiva, anogenital area); •Can rapidly evolve with blister or bullae formation; •May eventually evolve to epidermal detachment and/or necrosis *Systemic Symptoms:* fever, tachycardia, malaise, myalgia, arthralgia *Complications:* ↓ oral intake → fluid depletion; bacterial or fungal superinfection; multiorgan failure	NVP: 0.3% to 1% DLV & EFV: 0.1% 1-2 case reports for ABC, f-APV, ddI, ZDV, IDV, LPV/r, ATV	NVP – Female, Black, Asian, Hispanic	•2-week lead in period with 200mg once daily, then escalate to 200mg twice daily •Educate patients to report symptoms as soon as they appear •Avoid use of corticosteroid during NVP dose escalation – may increase incidence of rash	•Discontinue all ARVs and any other possible agent(s) (e.g., cotrimoxazole) Aggressive symptomatic support may include: •Intensive care support •Aggressive local wound care (e.g., in a burn unit) •Intravenous hydration •Parenteral nutrition, if necessary •Pain management •Antipyretics •Empiric broad-spectrum antimicrobial therapy if superinfection is suspected Controversial management strategies: •Corticosteroid •Intravenous immunoglobulin **Do not rechallenge patient with offending agent** ▪It is unknown whether patients who experienced SJS while NNRTI are more susceptible to SJS from another NNRTI – most experts would suggest avoiding use of this class unless no other option available
Hypersensitivity reaction (HSR)	ABC	Onset of 1st reaction: median onset – 9 days; approximately 90% within 1st 6 weeks Onset of rechallenge reactions: within hours of rechallenge dose Symptoms: acute onset of symptoms (in descending frequency): high fever, diffuse skin rash, malaise, nausea, headache, myalgia, chills, diarrhea, vomiting, abdominal pain, dyspnea, arthralgia, respiratory symptoms (pharyngitis, dyspnea/tachypnea) *With continuation of ABC, symptoms may worsen to include*: hypotension, respiratory distress, vascular collapse *Rechallenge reactions:* generally greater intensity than 1st reaction, can mimic anaphylaxis	Approximately 8% in clinical trial (2-9%); 5% in retrospective analysis	•HLA-B*5701, HLA-DR7, HLA-DQ3 (from Australian data) •ARV-naïve patients •Higher incidence of grade 3 or 4 HSR with 600mg once daily dose than 300mg twice daily dose in one study (5% vs. 2%)	•Educate patients about potential signs and symptoms of HSR and need for reporting of symptoms promptly •Wallet card with warning information for patients	•Discontinue ABC and other ARVs •Rule out other causes of symptoms (e.g., intercurrent illnesses such as viral syndromes, and other causes of skin rash, etc) •Most signs and symptoms resolve 48 hours after discontinuation of ABC *More severe cases:* •Symptomatic support – antipyretic, fluid resuscitation, pressure support (if necessary) •**Do not rechallenge patients with ABC after suspected HSR**

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Table 17. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations

17a. Potentially Life-Threatening and Serious Adverse Events (continued)

Adverse effects	Causative ARVs	Onset/clinical manifestation	Estimated frequency	Risk Factors	Prevention/ monitoring	Management
POTENTIALLY SERIOUS ADVERSE EFFECTS (listed in alphabetical order)						
Bleeding episodes – increase in hemophiliac patients	PIs	Onset: few weeks Symptoms: ↑ spontaneous bleeding tendency – in joints, muscles, soft tissues, and hematuria	Frequency unknown	• PI use in hemophiliac patients	• Consider using NNRTI-based regimen • Monitor for spontaneous bleeding	• May require increase use of Factor VIII products
Bone marrow suppression	ZDV	Onset: few weeks to months Laboratory abnormalities: • Anemia • Neutropenia Symptoms: fatigue because of anemia; potential for increase bacterial infections because of neutropenia	Anemia -1.1 to 4% Neutropenia – 1.8-8%	• Advanced HIV • High dose • Pre-existing anemia or neutropenia; • Concomitant use of bone marrow suppressants (such as cotrimoxazole, ribavirin, ganciclovir, etc.)	Avoid use in patients at risk Avoid other bone marrow suppressants if possible Monitor CBC with differential at least every three months (more frequently in patients at risk)	• Switch to another NRTI if there is alternative option; • Discontinue concomitant bone marrow suppressant if there is alternative option; otherwise: For neutropenia: • Identify and treat other causes • Consider treatment with filgrastim For anemia: • Identify and treat other causes of anemia (if present) • Blood transfusion if indicated • Consider erythropoietin therapy
Hepatotoxicity (clinical hepatitis or asymptomatic serum transaminase elevation)	All NNRTIs; All PIs; All NRTIs	Onset: NNRTI – for NVP - 2/3 within 1st 12 weeks NRTI – over months to years PI – generally after weeks to months Symptoms/Findings: **NNRTI** – asymptomatic to non-specific symptoms such as anorexia, weight loss, or fatigue. Approximately ½ of patients with NVP-associated symptomatic hepatic events present with skin rash. **NRTI** – • ZDV, ddI, d4T - may cause hepatotoxicity associated with lactic acidosis with microvesicular or macrovesicular hepatic steatosis because of mitochondrial toxicity • 3TC, FTC, or tenofovir – HBV co-infected patients may develop severe hepatic flare when these drugs are withdrawn or when resistance develops. **PI** – • Clinical hepatitis & hepatic decompensation have been reported with TPV/RTV. Underlying liver disease increases risk. • Generally asymptomatic, some with anorexia, weight loss, jaundice, etc.	Varies with the different agents	• Hepatitis B or C co-infection • Alcoholism • Concomitant hepatotoxic drugs • For NVP-associated hepatic events – female w/ pre-NVP CD_4 >250cells/mm^3 or male w/ pre-NVP CD_4 >400cells/mm^3	NVP – monitor liver associated enzymes at baseline, 2 & 4 weeks, then monthly for 1st 3 months; then every 3 months TPV/RTV- contraindicated in patients with moderate to severe hepatic insufficiency; for other patients follow "frequently" during treatment Other agents: monitor liver-associated enzymes at least every 3-4 months or more frequently in patients at risk	• Rule out other causes of hepatotoxicity – alcoholism, viral hepatitis, chronic HBV w/ 3TC, FTC or TDF withdrawal, or HBV resistance, etc. For symptomatic patients: • Discontinue all ARV (with caution in patients with chronic HBV infection treated w/ 3TC, FTC and/or TDF) and other potential hepatotoxic agents • After symptoms subside & serum transaminases returned to normal, construct a new ARV regimen without the potential offending agent(s) For asymptomatic patients: • If ALT > 5-10x ULN, some may consider discontinuing ARVs, others may continue therapy with close monitoring • After serum transaminases returned to normal, construct a new ARV regimen without the potential offending agent(s) **Note:** Please refer to information regarding NVP-associated symptomatic hepatic events & NRTI-associated lactic acidosis with hepatic steatosis in this table
Nephrolithiasis/ urolithiasis/ crystalluria	IDV – most frequent	Onset: any time after beginning of therapy – especially at times of reduced fluid intake Laboratory abnormalities: pyuria, hematuria, crystalluria; rarely – rise in serum creatinine & acute renal failure Symptoms: flank pain and/or abdominal pain (can be severe), dysuria, frequency	12.4% of nephrolithiasis reported in clinical trials (4.7% -34.4% in different trials)	• History of nephrolithiasis • Patients unable to maintain adequate fluid intake • High peak IDV concentration • ↑ duration of exposure	• Drink at least 1.5 to 2 liters of non-caffeinated fluid (preferably water) per day • Increase fluid intake at first sign of darkened urine • Monitor urinalysis and serum creatinine every 3-6 months	• Increase hydration • Pain control • May consider switching to alternative agent or therapeutic drug monitoring if treatment option is limited • Stent placement may be required

Table 17. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations

17a. Potentially Life-Threatening and Serious Adverse Events (continued)

Adverse effects	Causative ARVs	Onset/clinical manifestation	Estimated frequency	Risk Factors	Prevention/ monitoring	Management
POTENTIALLY SERIOUS ADVERSE EFFECTS (listed in alphabetical order)						
Nephrotoxicity	IDV, potentially TDF	Onset: IDV – months after therapy TDF – weeks to months after therapy Laboratory and other findings: IDV: ↑ serum creatinine, pyruria; hydronephrosis or renal atrophy TDF: ↑ serum creatinine, proteinuria, hypophosphatemia, glycosuria, hypokalemia, non-anion gap metabolic acidosis Symptoms: IDV: asymptomatic; rarely develop to end stage renal disease TDF: asymptomatic to signs of nephrogenic diabetes insipidus, Fanconi Syndrome	Not known	•History of renal disease •Concommitant use of nephrotoxic drugs	•Avoid use of other nephrotoxic drugs •Adequate hydration if on IDV therapy •Monitor serum creatinine, urinalysis, serum potassium and phosphorus in patients at risk	•Stop offending agent, generally reversible •Supportive care •Electrolyte replacement as indicated
Pancreatitis	ddI alone; ddI + d4T; ddI + hydroxyurea (HU) or ribavirin (RBV); 3TC in children	Onset: usually weeks to months Laboratory abnormalities: increased serum amylase and lipase Symptoms: post-prandial abdominal pain, nausea, vomiting	ddI alone – 1-7% ddI with HU - ↑ by 4-5 fold ddI with RBV, d4T or TDF - ↑ frequency 3TC in children – early trials: 14-18%; later trial - <1%	•High intraceullar and/or serum ddI concentrations •History of pancreatitis •Alcoholism •Hypertriglyceridemia •Concomitant use of ddI with d4T, HU, or RBV •Use of ddI + TDF without ddI dose reduction	•ddI should not be used in patients with history of pancreatitis •Avoid concomitant use of ddI with d4T, HU or RBV •Reduce ddI dose when used with TDF •Monitoring of amylase/lipase in asymptomatic patients is generally not recommended	•Discontinue offending agent(s) •Symptomatic management of pancreatitis – bowel rest, IV hydration, pain control, then gradual resumption of oral intake •Parenteral nutrition may be necessary in patients with recurrent symptoms upon resumption of oral intake
Skin rash	NVP > EFV, DLV; ABC, APV, f-APV, ATV, TPV/RTV	Onset: within first few days to weeks after initiation of therapy Symptoms: most rashes are mild to moderate in nature; diffuse maculopapular rash with or without pruritus; severe rash, rash with fever or with mucus membrane involvement warrants immediate discontinuation of ARV TPV-RTV - Rash accompanied by joint pain/ stiffness, throat tightness, or generalized pruritus have been reported. **Note**: Please also see sections on Stevens-Johnson Syndrome & Systemic Hypersensitivity Reaction	All Grades (severe) NVP: 14.8% (1.5% severe) EFV: 26% (1% grades 3- 4) DLV: 35.4% (4.4% grades 3-4) ABC: <5% in pts w/o HSR APV: 20-27% (1.0% grades 3-4) f-APV: 19% (< 1% grades 3-4) ATV: 21% (<1% severe) TPV/RTV 14% female & 8-10% male in Phase 2/3 trials; 33% in female HIV- subjects in Phase 1 study with ethinyl estradiol	• NVP – female, Black, Asian, Hispanic • f-APV, APV, TPV – sulfonamide derivative – potential for cross hypersensitivity with other sulfa drugs • TPV – female gender associated with an increased frequency of skin rash associated with TPV • EFV – higher incidence in children	•NVP – always use a 2-week low dose lead-in period •Avoid use of corticosteroid during NVP dose escalation – may increase incidence of rash •Patient education – advise to report first sign of rash •Most experts suggest avoidance of EFV or DLV in patients with history of severe rash from NVP, and vice versa	•Mild to moderate rash may be managed by symptomatic treatment with antihistamine and continuation of offending agent •Discontinue therapy if skin rash progresses to severe in nature (accompanied by blisters, fever, mucous membrane involvement, conjunctivitis, edema, or arthralgias) or in presence of systemic symptoms (including fever) **Do not restart offending medication in case of severe rash** •If rash develops during first 18 weeks of NVP treatment – obtain serum transaminases to rule out symptomatic hepatic event

Table 17. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations

17b. Adverse Events With Potential Long-Term Complications (listed in alphabetical order)

Adverse effects	Causative ARVs	Onset/clinical manifestation	Estimated frequency	Risk Factors	Prevention/ monitoring	Management
Cardiovascular effects	Possibly all PIs; maybe except for ATV	Onset: months to years after beginning of therapy Presentation: premature coronary artery disease	3-6 per 1000/pt years	Other risk factors for cardiovascular disease such as smoking, age, hyperlipidemia, hypertension, diabetes mellitus, family history of premature coronary artery disease and personal history of coronary artery disease	•Assess each patient's cardiac risk factors •Consider non-PI based regimen •Monitor & identify pts w/ hyperlipidemia or hyperglycemia •Counseling for life style modification - smoking cessation, diet, and exercise	•Early diagnosis, prevention, and pharmacologic management of other cardiovascular risk factors such as hyperlipidemia, hypertension, and insulin-resistance/diabetes mellitus •Assess cardiac risk factors •Lifestyle modifications: diet, exercise, and/or smoking cessation •Switch to agents with less propensity for increasing cardiovascular risk factors, ie NNRTI- or ATV-based regimen & avoid d4T use
Hyperlipidemia	All PIs (except ATV); d4T; EFV (to a lesser extent)	Onset: weeks to months after beginning of therapy Presentation: All PIs except ATV – ↑ in LDL & total cholesterol (TC) & triglyceride (TG), ↓ in HDL LPV/r & RTV – disproportionate ↑ in TG d4T – mostly ↑ in TG; may also have ↑ in LDL & total cholesterol (TC) EFV or NVP: ↑ in HDL, slight ↑ TG	Varies with different agents; 47% -75% of pts receiving PI in some clinics; Swiss Cohort: ↑TC & TG – 1.7-2.3x higher in pts receiving (non-ATV) PI	•Underlying hyperlipidemia •Risk based on ARV therapy PI: LPV/r & RTV > NFV & APV > IDV & SQV > ATV; NNRTI: less than PIs; NRTI: d4T > ZDV & TDF	•Use non-PI, non-d4T based regimen •Use ATV-based regimen •Fasting lipid profile at baseline, 3-6 months after starting new regimen, then annually or more frequently if indicated (in high risk patients, or patients with abnormal baseline levels)	•Follow ACTG guidelines's recommendations for management *[308]* •Assess cardiac risk factor •Lifestyle modification: diet, exercise, and/or smoking cessation •Switching to agents with less propensity for causing hyperlipidemia Pharmacologic Management: •↑ total cholesterol, LDL, TG 200-500 mg/dL: "statins" – pravastatin or atorvastatin (See **Tables 19 & 20** for Drug Interaction information) •TG > 500 mg/dL – gemfibrozil or micronized fenofibrate
Insulin resistance/ Diabetes mellitus	All PIs	Onset: weeks to months after beginning of therapy Presentation: Polyuria, polydipsia, polyphagia, fatigue, weakness; exacerbation of hyperglycemia in patients with underlying diabetes	Up to 3-5% of patients developed diabetes in some series	Underlying hyperglycemia, family history of diabetes mellitus	•Use PI-sparing regimens •Fasting blood glucose 1-3 months after starting new regimen, then at least every 3-6 months	•Diet and exercise •Consider switching to an NNRTI-based regimen •Metformin •"glitazones" •Sulfonylurea •Insulin
Osteonecrosis	All PIs	Clinical Presentation (generally similar to non-HIV population): •Insidious in onset, with subtle symptoms of mild to moderate periarticular pain •85% of the cases involving one or both femoral heads, but other bones may also be affected •Pain may be triggered by weight bearing or movement	Reported incidence on the rise. Symptomatic osteonecrosis: 0.08% to 1.33%; Asymptomatic osteonecrosis: 4% from MRI reports	•Diabetes •Prior steroid use •Old age •Alcohol use •Hyperlipidemia •Role of ARVs and osteonecrosis – still controversial	•Risk reduction (e.g., limit steroid and alcohol use) •Asymptomatic cases w/ < 15% bony head involvement – follow with MRI every 3-6 months x 1 yr, then every 6 mon x 1 yr, then annually – to assess for disease progression	Conservative management: • ↓ weight bearing on affected joint; • Remove or reduce risk factors • Analgesics as needed Surgical Intervention: •Core decompression +/- bone grafting – for early stages of disease •For more severe and debilitating disease – total joint arthroplasty

Table 17. Antiretroviral Therapy Associated Adverse Effects and Management Recommendations

17c. Adverse Effects Compromising Quality of Life and/or With Potential Impact on Medication Adherence (listed in alphabetical order)

Adverse effects	Causative ARVs	Onset/clinical manifestation	Estimated frequency	Risk Factors	Prevention/ monitoring	Management
Central nervous system effects	EFV	Onset: begin with first few doses Symptoms: may include one or more of the following: drowsiness, somnolence, insomnia, abnormal dreams, dizziness, impaired concentration & attention span, depression, hallucination; exacerbation of psychiatric disorders; psychosis; suicidal ideation Most symptoms subside or diminish after 2-4 weeks	> 50% of patients may have some symptoms	• Pre-existing or unstable psychiatric illnesses; • Use of concomitant drugs with CNS effects	• Take at bedtime or 2-3 hours before bedtime; • Take on an empty stomach to reduce drug concentration & CNS effects • Warn patients regarding restriction of risky activities – such as operating heavy machinery during the 1st 2-4 weeks of therapy	• Symptoms usually diminish or disappear after 2-4 weeks • May consider discontinuing therapy if symptoms persist and cause significant impairment in daily function or exacerbation of psychiatric illness
Fat maldistribution	PIs, d4T	Onset: gradual - months after initiation of therapy Symptoms: • Lipoatrophy – peripheral fat loss manifested as facial thinning, thinning of extremities and buttocks (d4T) • Increase in abdominal girth, breast size, and dorsocervical fat pad (buffalo hump)	High – exact frequency uncertain; increases with duration on offending agents	Lipoatrophy – low baseline body mass index	None to date	• Switching to other agents – may slow or halt progression, however, may not reverse effects • Injectable poly-L-lactic acid for treatment of facial lipoatrophy
Gastrointestinal (GI) intolerance	All PIs, ZDV, ddI	Onset: Begin within first doses Symptoms: • Nausea, vomiting, abdominal pain – all listed agents • Diarrhea – commonly seen with NFV, LPV/r, & ddI buffered formulations	Varies with different agents	All patients	• Taking with food may reduce symptoms (not recommended for ddI or unboosted IDV) • Some patients may require antiemetics or antidiarrheals pre-emptively to reduce symptoms	May spontaneously resolve or become tolerable with time; if not: For nausea & vomiting, consider: • Antiemetic prior to dosing • Switch to less emetogenic ARV For diarrhea, consider: • Antimotility agents – such as loperamide, diphenoxylate/atropine • Calcium tablets • Bulk-forming agents, such as psyllium products • Pancreatic enzymes In case of severe GI loss: • Rehydration & electrolyte replacement as indicated
Injection site reactions	Enfuvirtide	Onset: Within first few doses Symptoms: pain, pruritus, erythema, ecchymosis, warmth, nodules, rarely injection site infection	98%	All patients	Educate patients regarding use of sterile technique, ensure solution at room temperature before injection, rotate injection sites, avoid injection into sites with little subcutaneous fat or sites of existing or previous reactions	• Massaging area after injection may reduce pain • Wear loose clothing – especially around the injection site areas or areas of previous reactions • Rarely, warm compact or analgesics may be necessary
Peripheral neuropathy	ddI, d4T, ddC	Onset: weeks to months after initiation of therapy (may be sooner in patients with pre-existing neuropathy) Symptoms: • Begins with numbness & paresthesia of toes and feet; • May progress to painful neuropathy of feet and calf; • Upper extremities less frequently involved • Can be debilitating for some patients. • May be irreversible despite discontinuation of offending agent(s)	ddI: 12-34% in clinical trials d4T: 52% in monotherapy trial ddC: 22-35% in clinical trials Incidence increases with prolonged exposure	• Pre-existing peripheral neuropathy; • Combined use of these NRTIs or concomitant use of other drugs which may cause neuropathy • Advanced HIV disease • High dose or concomitant use of drugs which may increase ddI intracellular activities (e.g., HU or RBV)	• Avoid using these agents in patients at risk – if possible • Avoid combined use of these agents • Patient query at each encounter	• May consider discontinuing offending agent before pain becomes disabling – may halt further progression, but symptoms maybe irreversible Pharmacological management (with variable successes): • Gabapentin (most experience), tricyclic antidepressants, lamotrigine, oxycarbamazepine (potential for CYP interactions), topiramate, tramadol • Narcotic analgesics • Capsaicin cream • Topical lidocaine